## REMARKS

Favorable reconsideration is respectfully requested.

The claims are 1 to 6 and 8 to 25.

The above amendment is responsive to points set forth in the Official Action.

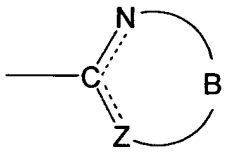
Points to note in this regard are as follows:

1. On the rejection of Claims 1 and 17 under 35 U.S.C. 112, second paragraph on the ground of indefiniteness:

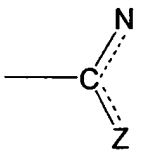
1-1. The rejection states in Official Action, page 2, paragraph (a), " . . . the claim language is unclear as to the number or range of atoms included in the 'remainder of the group' of variable group B". The phrase "remainder of the group" indicated by the rejection occurs in the definition of B, which is as follows:

> "B stands for the residual member(s) necessary for completing a monocyclic or polycyclic, nitrogen-containing heterocyclic group, which may form a condensed ring together with the remainder of the group of the above formula . . "

The phrase "the above formula" in the above-quoted definition means a moiety of the following formula:




which is denoted by Ar. Hence, "the remainder of the group of the above formula" clearly means the following:




Firstly, the reason why B in Claim 1 is defined as quoted above is explained below.

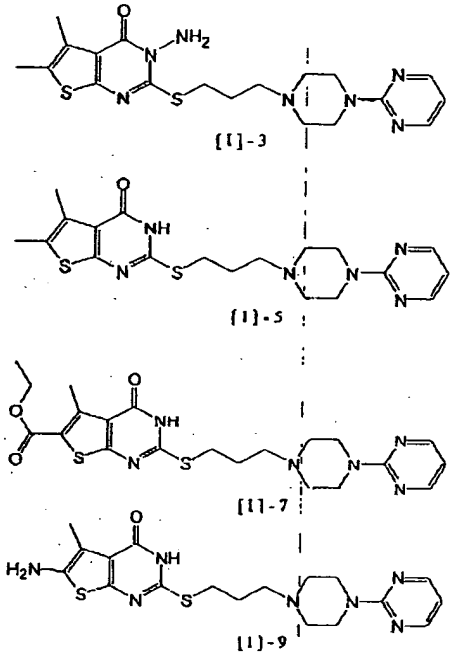
Before the present application was filed, it had already been publicly known that a compound whose portion of the above formula was a substituted phenyl group showed 5-$HT_{1A}$

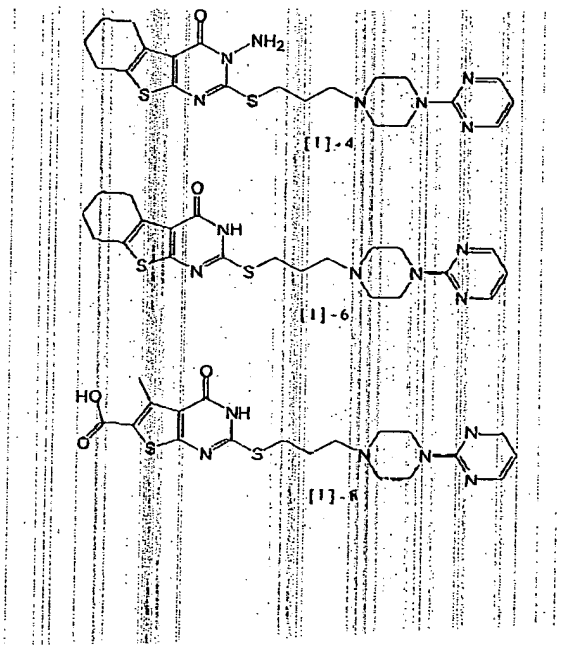
agonistic activity (although said compound was different from the compounds of the present invention in the other portions). It was, however, unknown whether said compound also had 5-$HT_3$ antagonistic activity.

Furthermore, a compound whose portion of the above formula was pyrimidine had also been known (among the documents cited in the outstanding Official Action, Bioorganic & Medicinal Chemistry Letters 10 (2000) 1089-1092 and Journal of Computer-Aided Molecular Design, 14(7), 647-657 (2000) refer to compounds which have a pyrimidine structure).

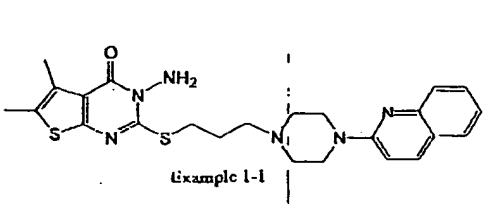
With regard to these compounds as well, it was only known that they had 5-$HT_{1A}$ agonistic activity, and it was quite unknown whether they had 5-$HT_3$ antagonistic activity.

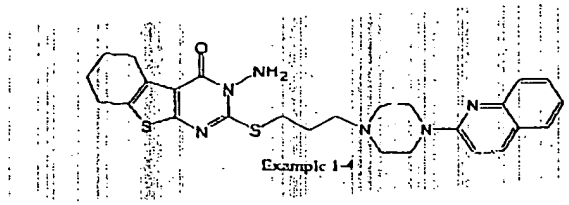
Under these circumstances, the present inventors synthesized compounds ([I]-3 to [I]-9) whose portion of the above formula was pyrimidine, as follows:




and measured these compounds for affinity to 5-$HT_{1A}$ receptor and to 5-$HT_3$ receptor. As a result, it was found that these compounds were equivalent in affinity to 5-$HT_{1A}$ receptor, but were much inferior in affinity to 5-$HT_3$ receptor to, i.e. compounds whose structure was similar to that of the above compounds ([I]-3 to [I]-9), but whose portion of the above formula was quinoline, i.e. the compounds of Example 1-1 and Example 1-4 of the present specification, as follows:

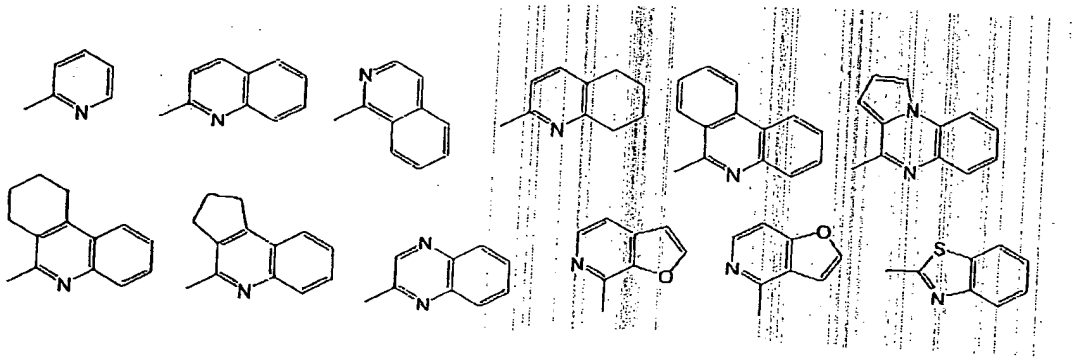



Enclosed herewith is the Rule 132 Declaration of T. Matsui, the second named inventor herein, which shows the above-mentioned experiment and its results. Although this Declaration was recently executed, the above-mentioned experiment *per se* had already been conducted before this application was filed.

As a result of assiduous study in view of the above-mentioned circumstances and the results of the above-mentioned experiment, the present inventors have found that, in order that both 5-$HT_{1A}$ agonistic activity and 5-$HT_3$ antagonistic activity may be exhibited, it is essentially necessary that the nitrogen atom should be next to carbon atom in the "above formula", and that Z should denote carbon, oxygen or sulfur. Thereby, the present inventors finally produced the compounds of the present invention.

Furthermore, the present specification gives 214 Examples, compounds of which have a portion of said "above formula" in a wide and representative range as follows:



In order to cover the various partial structures as mentioned above, the inventors used the expression of "above formula". It is considered that said expression suitably includes the above-mentioned various partial structures, and is appropriately enabled and definite.

Thus, the present inventors have adequately defined the "above formula" as explained above. It is considered that this definition appropriately defines the scope of the present claims.

1-2. With regard to Claim 17, the Official Action states at page 2, paragraph (b), ". . . therapeutic method of irritable bowel syndrome is unclear because as written, it implies that it is a method to induce IBS instead of treating it".

In reply, Claim 17 has been amended as follows:

- - A method for treating irritable bowel syndrome (IBS) - -

The Official Action further states, "It appears that this claim was literally translated from the original Japanese, resulting in a nonsensical claim. Cancellation is recommended". Claim 17, however, now recites "treating a disease by the cooperation of 5-$HT_{1A}$ agnostic activity and 5-$HT_3$ antagonistic activity" which is the essential feature of the present invention.

Accordingly, Claim 17 as amended is entirely appropriate.

2. On the rejection of Claims 16 to 22 under 35 U.S.C. 112, first paragraph on lack of enablement, the disease to be treated in Claims 16 and 25 is now defined as irritable bowel syndrome (IBS).

IBS is developed as a result of mutual association of intestinal motion disorder, viscerosensory anaphylaxis and psychological and social factors (see the present specification, page 1, lines 18 to 21). It is therefore effective to exert mental activity based on 5-$HT_{1A}$ agnostic activity and the enteric activity based on 5-$HT_3$ antagonistic activity in a living body (see the present specification, page 2, line 35 to page 3, line 4).

For the activity of compounds, the present specification gives at pages 45 to 56 the following five pharmacological tests:

(1) Measurement of affinity of the compounds to human 5-$HT_{1A}$ receptor (*in vitro*),

(2) Measurement of affinity of each test compound to human 5-$HT_3$ receptor (*in vitro*),

(3) Measurement of 5-$HT_{1A}$ receptor agnostic on rats (*in vivo*) behaviors of the lower lip retraction (LLP) and flat body posture (FBP),

(4) Measurement of 5-$HT_3$ receptor antagonistic action on rats (*in vivo*) BJ reflex inhibition, and

(5) Measurement of defecation acceleration in rats under restraint stress.

The above-recited pharmacological tests verify that the compounds of the present invention have 5-$HT_{1A}$ agonistic activity and 5-$HT_3$ antagonistic activity both *in vitro* and *in vivo*.

Among the above, (5) is known to be a test with use of a model of IBS (see Exhibits A and B attached, i.e. copies of two documents on IBS: Gastroenterology 1988; 94: 611-21 and the Journal of Pharmacology and Experimental Therapeutics 322: 1315-1323, 2007).

Thus, the present specification fully supports the fact that the compounds of the present invention are effective for the treatment of IBS.

Such being the case, the recitation of disease in Claims 16 and 25 as IBS overcomes the above rejection.

3. On the rejection under 35 U.S.C. 103 over Matsuoka et al. (CA 2431406):

3-1. In the above amended Claims, hydrogen has been deleted from the definition of $X^1$ of formula (I) of Claim 1. In other words, compounds wherein the 3-position of pyrimidine ring is unsubstituted are excluded from the scope of the present claims, and the compounds of the present claims are now directed to those wherein the 3-position of pyrimidine ring is substituted with (substituted) amino group, (substituted) alkyl group or (substituted) phenyl group.

3-2. In all of the compounds that are mentioned in Matsuoka, et al. (CA 2431406), the 3-position of pyrimidine ring is unsubstituted. Therefore, the above amendment clearly and unobviously distinguishes the compounds of the present claims from those of Matsuoka et al.

Furthermore, Matsuoka et al. teach or suggest nothing as to whether the compounds mentioned therein have 5-$HT_{1A}$ agonistic activity and/or 5-$HT_3$ antagonistic activity. Nor is it mentioned at all in Matsuoka et al. whether the compounds are effective against IBS.

Accordingly, compounds of the present claims are patentably distinguished from Matsuoka et al., both structurally and pharmacologically, and are therefore unobvious over Matsuoka et al.

3-3. With regard to the 35 U.S.C. 103 rejections over Modica et al. (Bioorganic & Medicinal Chemistry Letters 10(10), 1089-1092 (2000)) and Guccione et al. (Journal of Computer-Aided Molecular Design, 14(7), 647-657 (2000)), in all of the compounds of these references, the terminal heterocycle is a pyrimidine ring.

As stated in above 1-1, compounds which have a pyrimidine ring at their terminal are weak in 5-$HT_3$ antagonistic activity, and can be said to be unsuitable for the treatment of IBS

which is to be effectively treated by the cooperation of 5-$HT_{1A}$ agonistic activity and 5-$HT_3$ antagonistic activity (see attached Declaration).

Furthermore, Modica et al. and Guccione et al. teach or suggest nothing as to whether their compounds have 5-$HT_3$ antagonistic activity, and make no mention at all of the effects of the compounds on IBS.

Therefore, the compounds of the present invention are also unobvious over Modica et al. and Guccione et al.

No further issues remaining, allowance of this application is respectfully requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact undersigned at the telephone number below.

Respectfully submitted,

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